# ATENT COOPERATION TREAT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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# PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)* 12.01.2005

Applicant's or agent's file reference
PC/CP/P12998PC

**IMPORTANT NOTIFICATION**

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/GB 03/03199 | 28.07.2003 | 26.07.2002 |

Applicant
UNIVERSITY COURT OF THE UNIVERSITY OF EDINB..et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>PC/CP/P12998PC | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No.<br>PCT/GB 03/03199 | International filing date *(day/month/year)*<br>28.07.2003 | Priority date *(day/month/year)*<br>26.07.2002 |

International Patent Classification (IPC) or both national classification and IPC
C07K14/765

Applicant
UNIVERSITY COURT OF THE UNIVERSITY OF EDINB..et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| | |
|---|---|
| Date of submission of the demand<br>25.02.2004 | Date of completion of this report<br>12.01.2005 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Paresce, D<br>Telephone No. +49 89 2399-8995 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/03199

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

1-35 as originally filed

**Sequence listings part of the description, Pages**

1-7 as originally filed

**Claims, Numbers**

1-18 filed with the demand

**Drawings, Sheets**

1-19 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY EXAMINATION REPORT**

International application No. PCT/GB 03/03199

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-2, 4-16 |
| | No: | Claims | 3, 7-18 |
| Inventive step (IS) | Yes: | Claims | 1-2, 4-16 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-18 |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

**INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB 03/03199

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D1: WO 02/05645 A (NEW CENTURY PHARMACEUTICALS) 24 January 2002 (2002-01-24)

D2: WO 99/28348 A (RUKER FLORIAN ;HO JOSEPH X (US); CARTER DANIEL C (US); NEW CENTURY) 10 June 1999 (1999-06-10)

D1 (W0205645) discloses a modified serum albumin in which the affinity to trace metals such as nickel and/or copper is reduced or eliminated. The modified serum albumin is either truncated by at least one amino acid at its n-terminal end or is mutated in such a way as to disrupt the metal binding site of the serum albumin binding site VI. Mutations to this binding site include elongation, insertion or other changes to the n-terminal end, such as to the histidine at amino acid position 3, which either sterically hinder the binding site VI or eliminate vital binding interactions, and thus reduce the affinity of this region to metals such as nickel or copper.

D2 (W09928348) discloses a recombinant serum albumin which has been modified from human serum albumin, in the heme binding region, so as to have the ability when bound to heme to be capable of reversibly binding oxygen. In the disclosed modified albumin at least one of the hydrophobic binding residues responsible for the binding of heme in the serum albumin-heme binding region is replaced with a hydrophilic amino acid residue which is histidine or glutamine.

The IPEA is of the opinion that the modified serum albumins disclosed in D1 or D2 would fall under the scope of claims 3, 17-18. The scope of claim 3 is broad and unclear (see below) and therefore, could encompass the modified serums disclosed in the prior art. The method of claims 17-18 has been previously described in examples 1-2, p. 12-13 of D1 or example 1, p. 16-17 of D2.

The subject-matter of claims 1-2, 4-16 has not been made available to the public by any of the available prior art documents and can therefore be regarded as novel. The subject-matter of claims 1-2, 4-16 cannot be derived from the available prior art in an obvious manner and therefore complies with the requirements of Article 33(3) PCT.

**INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB 03/03199

The expression "substantially" used in claims 1, 3, 5 is not suitable to clearly define the scope of the claim, because it is without technical significance and its vagueness makes it entirely open to individual interpretation.

Claims 3, 18 contain references to the description and/or the drawings (i.e. to Table 1). According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

## CLAIMS

1. An isolated mutant human serum albumin substantially comprising the amino acid sequence:

DAHKSEVAHRFKDLGEENFKALVLIAFAQX$_5$LQQCPFEDHV
KLVNEVTEFAKTCVADESAENCDKSLX$_1$TLFGDKLCTVATL
RETYGEMADCCAKQEPERX$_2$X$_8$CFX$_6$QHKDDNPNLPRLVRPE
VDVMCTAFHDNEETFLKKYLYEIARRX$_9$PYFYAPELLFFAKR
YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKC
ASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK
VX$_{10}$TECCX$_3$X$_7$X$_4$LLECADDRADLAKYICENQDSISSKLKEC
CEKPLLEKSX$_{11}$CIAEVENDEMPADLPSLAADFVESKDVCKN
YAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLE
KCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLG
EYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCK
HPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES
LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQ
IKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKAD
DKETCFAEEGKKLVAASQAALGL

wherein $X_1$, is other than H; $X_2$ is other than N, $X_3$ is other than H, $X_4$ is other than D; $X_5$ is other than Y; $X_6$ is other than L; $X_7$ is other than G, $X_8$ is other than E, $X_9$ is other than H, $X_{10}$ is other than H, and $X_{11}$ is other than H, such that said mutant displays an altered metal binding affinity and/or other physiological characteristic(s) with respect to native human serum albumin.

2. The mutant according to claim 1 wherein the other physiological characteristic(s) are a change in cell adhesion to a substrate, percentage viability of cell and/or cell growth of cells in culture.

3. An isolated mutant mammalian serum albumin substantially comprising one of the sequences as shown in Table 1 wherein at least one of the residues identified by grey-shading is mutated such that said mutant serum albumin displays an altered metal binding affinity or other physiological characteristic(s) with respect to the native sequence from which the mutant is derived.

4. An isolated mutant serum albumin according to any preceding claim which is at least 90% identical with the native sequence from which the mutant is derived.

5. The mutant serum albumin according to any preceding claim which is substantially similar in terms of general overall folding with respect to the native serum albumin from which it is derived.

6. The mutant serum albumin according to any preceding claim wherein the altered metal binding affinity is a decrease or increase in metal binding affinity.

7. The mutant according to any preceding claim wherein the metal is zinc.

8. The mutant according to any preceding claim comprising at last one of the following mutations:

$X_1 \Rightarrow$ A, F, G, I, K, L, N, P, Q, R, S, T, V, W, Y, C, D, E

$X_2 \Rightarrow$ A, F, G, I, K, L, P, Q, R, S, T, V, W, Y, C, D E, H

$X_3 \Rightarrow$ A, F, G, I, K, L, N, P, Q, R, S, T, V, W, Y, C, D, E

$X_4 \Rightarrow$ A, F, G, I, K, L, N, P, Q, R, S, T, V, W, Y, C, E, H

$X_5 \Rightarrow$ C, D, E, H

$X_6 \Rightarrow$ C, D, E, H

$X_7 \Rightarrow$ C, D, E, H

$X_8 \Rightarrow$ A, C, F, G, H, I, K, L, N, P, Q, R, S, T, V, W, Y

$X_9 \Rightarrow$ A, D, E, F, G, I, K, L, N, P, Q, R, S, T, V, W, Y

$X_{10} \Rightarrow$ A, D, E, F, G, I, K, L, N, P, Q, R, S, T, V, W, Y

$X_{11} \Rightarrow$ A, D, E, F, G, I, K, L, N, P, Q, R, S, T, V, W, Y

9. The mutant according to any preceding claim comprising at least one mutation at $X_1$, $X_2$, $X_3$ or $X_4$.

10. A mutant human serum albumin comprising the mutation Asn 99His, Asn99Asp or His67Ala.

11. A nucleic acid sequence capable of encoding a mutant serum albumin according to any preceding claim.

12. An expression cassette comprising a promoter operably linked to a nucleic acid sequence according to claim 11.

13. A pharmaceutical composition comprising a mutant serum albumin, a nucleic acid sequence or an expression cassette according to any preceding claim and a pharmaceutically acceptable carrier therefore.

14. A cell culture medium comprising a mutant serum albumin, a nucleic acid sequence or an expression cassette according to any one of claims 1 – 12.

15. Use of a mutant serum albumin, nucleic acid or expression cassette according to any one of claims 1 – 12 in culturing of cells for affecting cell adhesion and/or cell growth characteristics.

16. A method of altering growth characteristics of cells in cell culture comprising the step of culturing cells in cell culture in the presence of a mutant serum albumin according to any one of claims 1-12.

17. A method of obtaining a mutant serum albumin which displays an altered metal binding affinity and/or other physiological characteristic(s) with respect to a native albumin from which the mutant has been derived, comprising the steps of:

a) providing a nucleic acid sequence encoding a nucleic albumin polypeptide;

b) conducting a mutagenisis reaction on said nucleic acid in order to alter said nucleic acid whereby said altered nucleic acid sequence encodes a mutant albumin polypeptide comprising at least one mutation with respect to said native albumin;

c) expressing said mutant albumin polypeptide and detecting whether or not said mutant albumin displays an altered metal binding and/or other physiological characteristic(s).

18. The method according to claim 17 wherein the mutant albumin comprises at least one mutation to residues $X_1 - X_{11}$ as shown in Table 1.

**BEFORE THE OFFICE OF ENROLLMENT AND DISCIPLINE**
**UNITED STATES PATENT AND TRADEMARK OFFICE**

## LIMITED RECOGNITION UNDER 37 CFR § 11.9(b)

Richard G. A. Bone is hereby given limited recognition under 37 CFR §11.9(b) as an employee of Morgan, Lewis & Bockius LLP, to prepare and prosecute patent applications wherein the patent applicant is the client of Morgan, Lewis & Bockius LLP and the attorney or agent of record in the applications is a registered practitioner who is a member of Morgan, Lewis & Bockius LLP. This limited recognition shall expire on the date appearing below, or when whichever of the following events first occurs prior to the date appearing below: (i) Richard G. A. Bone ceases to lawfully reside in the United States, (ii) Richard G. A. Bone's employment with Morgan, Lewis & Bockius LLP ceases or is terminated, or (iii) Richard G. A. Bone's employment authorization ceases or expires.

This document constitutes proof of such recognition. The original of this document is on file in the Office of Enrollment and Discipline of the U.S. Patent and Trademark Office.

**Expires: November 11, 2005**

Harry I. Moatz
Director of Enrollment and Discipline